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Use of NOACs in the Perioperative Management of Patients with Atrial Fibrillation: To Stop, Bridge or Continue?

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Over the last decade the availability of non-vitamin K antagonist oral anticoagulants (NOACs) has significantly changed daily clinical practice in managing thromboembolic risk in patients with atrial fibrillation (AF)(1). Guidelines for AF management have established that NOACs are the preferred treatment for the majority of AF patients (2); however recent data from “real-life” registries clearly shows that a significant proportion of patients are still treated with vitamin K antagonists (VKA)(3–5). Nevertheless, the role of NOACs still seems to be debated in some specific circumstances, such as their role in the perioperative management of patients with AF, in relation to interruption or continuation of anticoagulation.

The management of oral anticoagulation (OAC) therapy in the perioperative setting, has been long debated. Despite the absence of solid evidence, bridging OAC therapy with unfractionated heparin or low molecular weight heparin (LMWH) was commonly suggested (8). In 2015, the “Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery” (BRIDGE) trial provided an answer to this important issue regarding warfarin(9), demonstrating that while patients undergoing bridging therapy with LMWH had a similar risk for thromboembolic complications, they were at significantly increased risk of major bleeding(9). Although, there has been some clarification about periprocedural management with warfarin, uncertainty still remained about periprocedural NOAC management, due to the lack of solid data and limited clinical experience.

In this issue of *Thrombosis and Haemostasis*, Douketis and colleagues present a subgroup analysis on perioperative management and outcomes in AF patients

Comment [GL1]: Remove 4 and 5, change to the following

[Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in "real-world" clinical practice. A propensity-matched analysis of 76,940 patients.](#)

Li XS, Deitelzweig S, Keshishian A, Hamilton M, Horblyuk R, Gupta K, Luo X, Mardekian J, Friend K, Nadkarni A, Pan X, Lip GYH. *Thromb Haemost.* 2017 Jun 2;117(6):1072-1082.

[Dabigatran in real-world atrial fibrillation. Meta-analysis of observational comparison studies with vitamin K antagonists.](#)

Carmo J, Moscoso Costa F, Ferreira J, Mendes M. *Thromb Haemost.* 2016 Sep 27;116(4):754-63.

[Regional Differences in Antithrombotic Treatment for Atrial Fibrillation: Insights from the GLORIA-AF Phase II Registry.](#)

Mazurek M, Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, Halperin JL, Ma CS, Zint K, Elsaesser A, Lu S, Lip GYH; GLORIA-AF Investigators. *Thromb Haemost.* 2017 Dec;117(12):2376-2388.

[Effectiveness and Safety of Non-Vitamin K Oral Anticoagulants in Comparison to Phenprocoumon: Data from 61,000 Patients with Atrial Fibrillation.](#)

Höhnloser SH, Basic E, Hohmann C, Nabauer M. *Thromb Haemost.* 2018 Mar;118(3):526-538

treated with warfarin or edoxaban, derived from the “Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48” (ENGAGE AF-TIMI 48) trial(10). Of the 21,105 patients originally enrolled in the trial, 7193 (34.1%) required surgery or an invasive procedure, and were equally randomized to warfarin, edoxaban high dose (60 or 30 mg) and edoxaban low dose (30 or 15 mg), with no major differences across the three groups. The most common procedures were cardiac, gastrointestinal endoscopy, dental and electrophysiological. Among those undergoing elective procedures, 3116 (43.3%) had their anticoagulation interrupted, defined as warfarin/edoxaban stopped for 4 to 10 days before the procedure, while 4077 (56.7%) were defined as “anticoagulant continued”, having stopped randomized treatment ≤ 3 days (or not stopped at all) before the procedure(10). A 30-day observation period was established to determine if there were differences in efficacy and safety between warfarin and the two doses of edoxaban in patients undergoing elective procedures, in patients with interrupted or continued anticoagulation treatment.

In the anticoagulant interrupted group, rates of stroke or systemic embolism at 30 days were 0.6%, 0.5% and 0.9% for the warfarin, edoxaban high dose and edoxaban low dose groups, respectively ($p=0.53$ for differences across the groups). Corresponding figures in the anticoagulation-continued group were 1.1%, 0.7% and 0.9%, with no significant between-group differences. Regarding the main safety outcome, major or clinically relevant non-major (CRNM) bleeding was reported in 3.9%, 4.2% and 3.6% of patients receiving warfarin, edoxaban high dose and edoxaban low dose, respectively for the anticoagulation interrupted group, with no significant differences across the three treatment groups. Among patients who

continued anticoagulation, rates of major/CRNM bleeding in the three treatment arms ($p=0.17$) were 8.5%, 7.9% and 6.6%, respectively. Mortality rates were similar across the three treatments whether or not anticoagulation was interrupted or continued(10). Results were comparable when analysed by type of procedure.

These results, strengthened by the sample size and the independently adjudicated outcomes, demonstrate that edoxaban can be safely used and managed in patients undergoing elective procedures but that safety appears to be improved if OAC is interrupted. These results, in particular comparing NOACs and warfarin in major adverse outcomes, reinforces and strengthens previous observations (Table) from subgroup analyses of other NOACs phase III trials, in patients undergoing elective procedures(11–13).

The current ESC AF guidelines do not provide specific recommendations about the management of OAC therapy in patients undergoing cardiovascular procedures and interventions, but suggest that these interventions can be performed safely on continued OAC and that on the basis of the BRIDGE trial discussed previously, bridging is not beneficial(2).

More recently, the European Heart Rhythm Association (EHRA) released a 2018 update to its practical guide on the use of NOACs in AF patients, which discussed this issue in greater detail(14), proposing perioperative management of OAC therapy as summarized in the Figure. The main points emphasised by the practical guide relate to patients' baseline characteristics, in particular age and renal function, as well as the theoretical bleeding risk carried by the specific procedure, which need to

Comment [GL2]: Not in colour

be taken into account when deciding whether to stop NOACs or not. Second, given the predictable effect and rapid clearance of NOACs, timely management of the planned procedure can take advantage of the window between dose administration(14).

Taking these aspects into consideration, in procedures with a minor bleeding risk (dental or eye procedures, diagnostic endoscopy and superficial surgery), all NOACs can be continued safely up to the day before the procedure. No NOACs are administered the morning of the procedure and in those cases performed with no adverse events and with an immediate and complete haemostasis, NOACs can be restarted at the subsequent programmed dose but not until 6 hours post-procedure(14).

In those procedures with a low bleeding risk (biopsies, electrophysiological or procedures with cardiac implantable devices, non-coronary angiographies), stop NOACs up to 24 hours before the procedure, and recommence based on the same conditions as for minor bleeding risk procedures(14). For all those subjects undergoing procedures with a high risk of bleeding (complex endoscopies, major surgeries) the recommendation is cessation of NOACs at least 48 hours before surgery, without bridging. In these situations, NOACs can be restarted 48 hours after the procedures (or longer in specific situations) or post- procedure low molecular weight heparin can be considered(14).

In patients treated with dabigatran before the procedure, it is recommended to perform an accurate evaluation of renal function. In patients with a creatinine

clearance (CrCl) ≤ 80 mL/min, dabigatran should be stopped 12 hours earlier than in those with normal renal function (>80 mL/min); 24 hours earlier in patients with CrCl ≤ 50 mL/min; 36 hours earlier in patients ≤ 30 mL/min. Similarly, in other specific situations in which the NOACs clearance could be prolonged it is recommended to stop the NOAC earlier(14).

Another recent review about use NOACs in surgical scenarios, proposed similar recommendations, underlining the importance of stratifying the procedure predicted bleeding risk and of knowing the expected clearance time of the specific NOAC in the context of patient's age and comorbidities(15).

Notwithstanding the results provided by the NOAC phase III trials and expert recommendations, there is still a need for more specific perioperative data from adequately powered randomized studies to provide definitive evidence, given the need to balance thromboembolic and bleeding risks in AF management [ref]. To address this, the "Perioperative Anticoagulant Use for Surgery Evaluation" (PAUSE) study has been initiated (ClinicalTrials.gov NCT02228798)(16), a prospective study with three parallel cohorts (dabigatran, rivaroxaban and apixaban), aiming to enrol 3291 patients undergoing surgical procedures, to establish if the suggested NOAC and patient specific interruption-resumption protocols are safe in the perioperative management of AF patients(16). Results from this study will provide stronger evidence about the management of NOACs in this specific setting.

Comment [GL3]: [A two-sided evaluation of benefit and harm from antithrombotic treatment in atrial fibrillation: Balancing clinical application and statistical methodology.](#)
Nielsen PB, Skjøth F.
Thromb Haemost. 2016 Aug 30;116(3):405-6.

CONCLUSIONS

Despite the availability of data from subgroup analyses of the NOACs phase III trials and expert recommendations to reassure clinicians about the efficacy and safety of NOACs in the perioperative management of AF patients (based on their predictability of anticoagulation effect, rapid clearance of effect), robust evidence from RCTs is still required to further clarify the risks associated with interruption or continuation of NOACs. Patient engagement, education and counselling are additional practical aspects to ensure safety whilst taking NOACs [ref].

Comment [GL4]: [Patient values and preferences for antithrombotic therapy in atrial fibrillation. A Narrative Systematic Review.](#)
Loewen PS, Ji AT, Kapanen A, McClean A.
Thromb Haemost. 2017 Jun 2;117(6):1007-1022.

Table: Evidence about Periprocedural Management of NOACs from Phase III Trials

STUDY	YEAR	NOAC	PATIENTS	PROCEDURES	TREATMENTS	RESULTS
Healey (11)	2012	Dabigatran	4591 (25.3%)	-	D110: 1487 D150: 1546 W: 1558	Stroke/SE <i>D110 vs W: RR 1.05 95% CI 0.55-2.01</i> <i>D150 vs W: RR 1.01 95% CI 0.35-2.87</i> Major Bleeding <i>D110 vs W: RR 0.83 95% CI 0.59-1.17</i> <i>D150 vs W: RR 1.09 95% CI 0.80-1.49</i>
Sherwood (12)	2014	Rivaroxaban	4692 (33.0%)	7555	R: 2165 W: 2527	Stroke/SE <i>R vs W: HR 0.74 95% CI 0.36-1.50</i> Major Bleeding <i>R vs W: HR 1.26 95% CI 0.80-2.00</i>
Garcia (13)	2014	Apixaban	5439 (29.9%)	9260	A: 2701 W: 2738	Stroke/SE <i>A vs W: OR 0.60 95% CI 0.32-1.12</i> Major Bleeding <i>A vs W: OR 0.85 95% CI 0.61-1.16</i>

Legend: A= Apixaban; CI= Confidence Interval; D110= Dabigatran 110 mg; D150= Dabigatran 150 mg; HR= Hazard Ratio; NOAC= Non-vitamin K Antagonist Oral Anticoagulant; OR= Odds Ratio; R= Rivaroxaban; RR= Relative Risk; SE= Systemic Embolism; W= Warfarin.

Figure Legends

Figure: Perioperative Management for NOACs in AF Patients

Legend: OAC treatment can be continued or restarted according to bleeding risk of the procedure (Solid blocks). In specific situations OAC can stopped later or restarted earlier if bleeding risk is considered particularly low or the procedure reported an immediate and complete haemostasis (Striped blocks). Under physicians' judgement thromboprophylaxis with LMWH can be considered (Dotted blocks). *In patients taking Dabigatran, drug must be stopped as much earlier as lower is the renal function; AF= Atrial Fibrillation; LMWH= Low Molecular Weight Heparin; NOACs= Non-vitamin K Antagonist Oral Anticoagulants.

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